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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,947	WOLFF ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-124* is/are pending in the application.

4a) Of the above claim(s) *12-18,20-27,47-62,75-79,99-102,108-112 and 118-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,28-46,63-74,80-98,103-107 and 113-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-11, 28-46, 63-74, 80-98, 103-107 and 113-117) in the reply filed on September 16, 2004) is acknowledged. It is noted that Applicant has elected not to pursue any of the specific sequences set forth in Groups II-VII, pending the allowability of the generic linking claim. The traversal is based on the following ground(s):

1. Applicant contends that a search of all of the nucleic acids set forth in the claims would not be burdensome because there is no indication that such a search would be more complex than any other sequence search. In support of this argument, Applicant cites MPEP §§ 803.04 and 2434, and suggests that an election of species would be a more appropriate form of restriction (see for example the second and third paragraphs of page 1).

2. Applicant argues that nucleic acid sequences and amino acid sequences are not unrelated, but are rather related in a "final-to-intermediate product" manner (see for example the bridging paragraph of pages 1 and 2 of Applicant's response).

This is not found persuasive for the following reasons:

1. First, it is noted that should the generic linking claim be found allowable, then the specific sequences (broken into Groups II-VIII) depending on the generic claim would also necessarily be allowable, in accordance with linking claim practice. As such, there would be no need to contest the rejoinder of the individual sequences should the generic claim be found allowable. However, as it regards the rejoinder of the sequences in the absence of an indication of an allowable linking claim, it is noted that restriction to a single sequence is in agreement with

current USPTO practice. The Commissioner's Office has partially waved the requirements of 37 CFR 1.141 based upon the acknowledgement that a search of multiple sequences is indeed burdensome to the Office; this was clearly set forth in the restriction requirement. Thus, Applicant's request that the sequences be rejoined because the search would not be burdensome is not convincing, and the restriction requirement is maintained.

Applicant's suggestion to treat the claims as species is not convincing. It is noted that the individual sequences are independent inventions that are not linked by a common structural feature; each sequence has a distinct nucleic acid sequence that shares no common structural element relating to their functions. Indeed, each of the specific nucleic acids either encodes a functionally unrelated protein, or represents promoter elements that have functionally unrelated structures. In the instant case, linking claim practice is proper because each of the independent inventions are linked by a claim broadly encompassing each individual nucleic acid, but without reciting a common structure-function element relating to each sequence.

2. Applicant's contention that nucleic acid sequences and amino acid sequences are final-to-intermediate products is not consistent with the definition of the relationship. In a final-to-intermediate product relationship, the intermediate product is converted into the final product by a biochemical reaction. In the instant case, when a protein is formed, the nucleic acid remains intact; there is no chemical reaction converting a polynucleotide acid into a polypeptide. As such, the relationship between a nucleic acid sequence and an amino acid sequence does not fit the definition of a final-to-intermediate product relationship. As such, the Office maintains that it has not erroneously characterized amino acid and nucleic acids as being unrelated, and the restriction requirement is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-18, 20-27, 47-62, 75-79, 99-102, 108-112 and 118-124 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 16, 2004.

Claims 1-11, 28-46, 63-74, 80-98,103-107 and 113-117 are under examination in the instant application.

Priority

Applicant's claim for domestic priority to US 60/274,650 under 35 U.S.C. § 119(e) is acknowledged.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. § 119(a)-(d). The certified copy has been filed in the instant Application.

Information Disclosure Statement

It is noted that the format of the Form PTO-1449 is unconventional, but it contains the necessary information to accurately indicate the references to be considered. Therefore, the information disclosure statement filed September 24, 2002 has been considered, and a signed and initialed copy of the modified form PTO-1449 is attached to this Office Action.

Specification

The disclosure is objected to because of the following informalities: Applicant amended the specification on August 2, 2002 to identify sequences properly with SEQ ID NOS. However, in making the amendments, Applicant appears to have missed amending the specification at several locations, including: page 56, lines 11-12; page 122, line 2; page 126, line 27; page 129, line 19.

Appropriate correction is required.

Claim Objections

Claim 45 is objected to because of the following informalities: claim 45 lacks a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 28-46, 63-74, 80-98,103-107 and 113-117 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a polynucleotide by its ability to regulate the dimorphic shift of a vast number of fungal species. The claims read on a broad genus of polynucleotides that must have a particular function.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a polynucleotide by function only, without any disclosed or known correlation between the elements and their function. The specification only provides teachings regarding a limited number of structurally unrelated polynucleotides, and their ability to regulate the dimorphic shift of fungal cells to which they are endogenous. The specification does not teach what structural features of the claimed polynucleotides (or the polypeptides which they encode) are sufficient or necessary to regulate dimorphic shift across a wide variety of fungal species. In other words, the skilled artisan cannot envision (a) which polynucleotides from other fungal species would have the ability the cause a dimorphic shift in non-endogenous species, or (b) which of the structurally unrelated polynucleotides taught in the instant specification have the capacity to regulate dimorphic shift outside of their endogenous organism.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. The prior art does not disclose structural or functional features of a polynucleotide that would allow the skilled artisan to envision a representative number of polynucleotides having the capacity to regulate dimorphic shift in a wide variety of fungal species. Indeed, the prior art provides examples of the claimed invention as it relates to regulating morphology within the endogenous fungal cell (see for example Sonneborn *et al.*, *Mol. Microbiol.* **35**: 386-396, in particular page 390, right hand column). However, due to the lack of a structure-function relationship, either in the prior art or the instant specification, the skilled artisan cannot envision whether or not these examples of polynucleotides will have the necessary function across a broad species of fungal cells, as required by the instant claims. With regard to the particular reference, the skilled artisan cannot envision if Ca*TPK2* will function to cause a dimorphic shift in *Mucor* species because neither the instant specification nor the prior art describes a domain that necessary confers that function. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Because neither the specification of the instant application or the prior art teaches a structure-function relationship for the claimed polynucleotides, the skilled artisan would not be able to envision the claimed invention. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 1-11, 28-46, 63-74, 80-98,103-107 and 113-117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide (and host cells containing said polynucleotide) having the ability to regulate the morphology of a dimorphic fungal cell in a fungal cell to which the polynucleotide is endogenous, does not reasonably provide enablement for a polynucleotide (and host cells thereof) that has the ability to regulate the morphology of *any* dimorphic fungal cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a polynucleotide, wherein the polynucleotide comprises two parts: first, it must encode a polypeptide having the ability to regulate the morphology of any dimorphic cell; second, it must be under the regulatory control of an element (e.g., a promoter) that does not normally regulate the transcription of the polynucleotide. In essence, the nucleic acid must encode a vast array of polypeptides, wherein these polypeptides are functional to elicit a dimorphic shift across a large number of fungal species. Thus, the skilled artisan must be aware of which polypeptides are functional, not only in

its endogenous organism, but in other dimorphic fungi as well. For example, the skilled artisan must be aware of what *S. cerevisiae* morphological regulators are functional in genetically diverse *Mucor* species, *Candida* species, *Yarrowia* species, etc. It is important to note the distinction that Applicant is claiming the polynucleotide, and not a method of causing a dimorphic shift in a fungal cell, and that the standard for enablement is the ability to make and use, not the ability to identify.

Breadth of the claims. The claims are very broad, reading on a polynucleotide having a function, but with no indication of what structural features of the polynucleotide are required to confer the functional ability to regulate dimorphic shift in a wide variety of fungi.

State of the art. The state of the art indicates that a few polynucleotides encoding polypeptides can regulate dimorphic shift in their endogenous species when expressed from a heterologous promoter. For instance, the expression of *TPK2* in *Candida* strains using the heterologous *PCK1* promoter results in a dimorphic shift of the host cell (see for example Sonneborn *et al.*, *Mol. Microbiol.* **35**: 386-396, in particular page 390, right hand column). However, the skilled artisan cannot predict if these polynucleotides have the ability to function across fungal species; i.e., one cannot predict the P_{PCK1}:*TPK2* construct causes a dimorphic shift in *Mucor* species. Thus, the state of the art indicates that polynucleotides encoding polypeptides with the ability to cause a dimorphic shift in its endogenous host cell, and that are also capable of causing such a shift in a genetically diverse species, cannot be predicted.

Indeed, even the instant specification recognizes that "there are large differences in the stimuli, regulation and control of the dimorphic shift" in different fungi (see for example page 5, lines 11-16). This suggests that the different genes involved in the signal transduction pathways

for dimorphic shift function differently, depending on the specific fungal cell. Thus, the skilled artisan would need to rely on specific teachings in the specification to ascertain which polynucleotides met the functional requirement to affect dimorphic shift in diverse species (or even in which particular species) of fungi.

Number of working examples and Guidance provided by applicant. The instant specification, aside from recognizing that different stimuli and regulatory factors affect dimorphic shift depending on the fungal species, does not describe which polynucleotides have the ability to function outside of their endogenous host cells to regulate dimorphic shift. The instant specification identifies *Mucor* orthologues of genes involved in dimorphic shift in different yeast, and indicates that these genes have the ability to affect dimorphic shift in the species from which they were isolated. However, there is no indication that these genes are functional in other fungal species that undergo dimorphic shift; i.e., there is no teaching suggesting that SEQ ID NO: 5 (*MPK1* isolated from *M. circinelloides*) will cause a dimorphic shift in *S. cerevisiae*. Nor is there any indication in the specification as to which genes involved in the dimorphic shift in *S. cerevisiae*, *C. albicans*, or any other dimorphic fungi will similarly cause a dimorphic shift in *M. circinelloides* (or even other *Mucor* species). Thus, the skilled artisan is left to ponder what known and unknown polynucleotides cause a dimorphic shift in which fungal species.

Unpredictability of the art and Amount of experimentation required. The instant invention is highly unpredictable across the broad range in which it is claimed, and would require an excessive amount of empirical, undue and unpredictable trial and error experimentation. The polynucleotide as claimed is required to have the functional capacity to regulate dimorphic shift

in both a broad range of host fungal cells, as well as in certain specific species. However, the skilled artisan is required to perform an inventive step: the determination of which polynucleotides have the required function, and in which organisms. Indeed, the skilled artisan cannot ascertain if polynucleotides already known in the art (e.g., P_{PCK1}:*TPK2* as indicated above) meet the limitations of certain claim embodiments, where the polynucleotide is required to function outside of its endogenous host fungal cell. Because the skilled artisan would have to empirically determine which polynucleotides were capable of regulating dimorphic shift in each fungal species, the invention is not considered to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claims 32, 40, 69, 70 and 84 (and their dependent claims), the phrase "including," which is equivalent to the term "for example," renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Specifically, it is unclear if the limitation of claim 69 is that the polynucleotide sequence form part of a signal transduction pathway in a microbial cell, if it must form a part of a signal transduction pathway in a fungal cell, etc. It would be remedial to recite the broadest limitation in an independent claim (whether that be a microbial cell, or something more specific), and then recite more specific limitations in dependent claims.

Claim 85 (and its dependent claims) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the phrases "and operably linked

thereto, and" and "comprising a further expression signal" in sections (i) and (ii) of the claim, respectively.

First, it is unclear what the phrase "and operably linked thereto, and" means because it is unclear what the "at least on nucleotide" is operably linked to; there is nothing explicitly indicated in the claim. Second, the term "further expression signal" appears to lack antecedent basis; the term "further" implies that there is at least one prior expression signal in the claim. However, there is no such recitation in the claims, thus it is unclear if there is a missing expression signal within the claim language, or if there is only one expression signal set forth in the claim. It would be remedial to indicate what is operably linked to the at least one nucleotide in section (i) and to indicate what other expression signal is a limitation in section (ii), or to amend the claims to remove the indefinite terms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It is noted that claims 32, 40, 69, 70 and 84 recite broad limitations, followed by narrow limitations preceded by the term "including" (for example, in claim 69, lines 4-5: "a microbial cell, including a fungal cell, including a *Mucor* species, including *M. circinelloides*"). It is unclear if the limitations following the term "including" are the actual limitations of the claims, or if the are merely examples that are within a broad claim limitation (see also the rejections

under 35 USC § 112, second paragraph). In the interest of compact prosecution, the claim is interpreted as broadly as reasonable, which means that the limitations following the term "including" are not given patentable weight. In other words, the broadest limitation set forth in the claim is considered the limitation that must be met because the term "including" does not appear to *exclude* other microbial species. Should Applicant wish the more specific examples to be the limitations of the claims, applicant is urged to clearly indicate that said specific examples are the limitations of the claims (i.e., indicate that the fungal cell must be a *Mucor* species, etc.).

Claims 1, 10, 11, 28-33, 40, 42-46, 63-67, 69-74, 80-86, 103-106, 113,115 and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Stoldt *et al.* (*EMBO J* **16**: 1982-1991, 1997; see entire document; henceforth Stoldt).

Stoldt teaches the identification of *EFG1*, a *Candida albicans* gene that regulates the morphological shift of the fungus from a budding growth form to the virulent hyphal form (see for example the Abstract and page 1983, left column, second full paragraph). Significantly, *EFG1* forms part of a MAP-kinase (camp-dependent) signal transduction cascade by virtue of its ability to regulate dimorphic shift in *Candida*, which relies on the MAP-kinase cascade for such a transition (see for example pages 1982-1983, bridging paragraph). Importantly, *EFG1* encodes a bHLH domain, implicating it as a transcriptional regulatory factor (see for example pages 1984-1985, bridging paragraph); thus, this regulator of morphology is capable of regulating transcription in a dimorphic fungal cell. Stoldt teaches fusing the *EFG1* gene to a heterologous promoter, specifically either the *GAL1* promoter (see for example 1984, right column, last full paragraph) or the *PCK1* promoter (see for example page 1987, left column to page1988, right

column). Thus, Stoldt teaches a chimeric polynucleotide, comprising a regulator of dimorphic shift in fungi operatively linked to a heterologous promoter element, wherein the regulator of dimorphic shift is at least capable of causing dimorphic shift in *Candida* (a uninucleated call having a unicellular essentially spherical morphology), and wherein the nucleic acid is derived from a eukaryotic microbial dimorphic fungal cell that undergoes filamentous growth under certain conditions. It is also important to note that the *GAL1* and *PCK1* promoter elements are induced/repressed by the composition of the growth medium (specifically, the type of carbon source, more specifically the presence/absence of galactose of glucose). Thus, by altering the presence or absence of galactose or glucose in the growth medium, one can increase or decrease the amount of the regulator that is produced.

Stoldt further teaches the transformation of this chimeric nucleic acid (in the form of an independently replicating episomal plasmid) into *Candida* cells (see for example page 1987, left column to page1988, right column, and Figure 6). Importantly, the episomal element used by Stoldt is a derivative of YEplac195 (see for example the Materials and Methods on page 1990), which carries both a 5' and 3' untranslated region. YEplac195 also comprises a bacterial ampicillin selectable marker and replication sequence, and is maintained at a high copy level (around 20-50 copies/nucleus) due to the presence of the 2μ element. Significantly, expression of the *EFG1* gene can be induced greater than 10-fold from the heterologous promoter (see for example Figure 6, lanes 7 and 8). Thus, Stoldt teaches the polynucleotide sequence of the indicated claims, as well as the cells that contain said polynucleotide sequence.

Claims 1, 10, 11, 28-33, 40-46, 63, 65-74, 80-86, 103-106, 113, 115 and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Sonneborn *et al.* (*Mol. Microbiol.* **35**: 386-396; see entire document; henceforth Sonneborn).

Sonneborn teaches the identification of *TPK2*, a *Candida albicans* gene (which is involved in the MAP kinase signaling cascade) that regulates the morphological shift of the fungus from a budding growth form to the virulent hyphal form (see for example the Abstract and page 390, left column). Sonneborn teaches fusing the *TPK2* gene to a heterologous promoter, specifically the *PCK1* promoter (see for example page 390, right column). Thus, Sonneborn teaches a chimeric polynucleotide, comprising a regulator of dimorphic shift in fungi operatively linked to a heterologous promoter element, wherein the regulator of dimorphic shift is at least capable of causing dimorphic shift in *Candida* (a uninucleated call having a unicellular essentially spherical morphology), and wherein the nucleic acid is derived from a eukaryotic microbial dimorphic fungal cell that undergoes filamentous growth under certain conditions. It is also important to note that the *PCK1* promoter element is induced/repressed by the composition of the growth medium (specifically, the type of carbon source, more specifically the presence/absence of galactose of glucose). Thus, by altering the presence or absence of galactose or glucose in the growth medium, one can increase or decrease the amount of the regulator that is produced.

Sonneborn further teaches the transformation of this chimeric nucleic acid (in the form of an independently replicating episomal plasmid) into *Candida* cells (see for example page 390, right column). Importantly, the episomal element used by Sonneborn is a derivative of YEplac195 (see for example the Materials and Methods on page 1990), which carries both a 5'

and 3' untranslated region. YEplac195 also comprises a bacterial ampicillin selectable marker and replication sequence, and is maintained at a high copy level (around 20-50 copies/nucleus) due to the presence of the 2μ element. Thus, Sonneborn teaches the polynucleotide sequence of the indicated claims, as well as the cells that contain said polynucleotide sequence.

Claims 85 and 103-107 are rejected under 35 U.S.C. 102(b) as being anticipated by Masuda *et al.* (*Curr. Genet.* **25**: 412-417, 1994; see entire document; henceforth Masuda).

It is noted that there is no requirement in these claims that the expressed polynucleotide encode a regulator of morphology. Rather, there is just a requirement that the nucleic acid be expressed in a cell capable of undergoing dimorphic shift, and that the expression of the polynucleotide be regulatable through a heterologous promoter element responsive to one or more environmental conditions.

Masuda teaches the expression of the *Kluyveromyces lactis* β-galactosidase gene (*LAC4*) from the *Candida maltosa PGK* promoter element (see for example the Abstract and Figure 3). Notably, the expression of the gene occurs *in C. maltosa*, which is a fungal cell that undergoes dimorphic shift. The *PGK* promoter is regulatable by the presence or absence of specific carbon sources in the growth medium (see for example page 413, right column, third full paragraph), wherein the amount of the gene product is substantially increased (>1.25 fold) in the presence of glucose (see for example Figure 2, lane 1 versus lanes 2-4). It is also important to note that β-galactosidase genes encode an N-terminal signal peptide that result in the secretion of the gene product from the host cell. Thus, Masuda anticipates the aforementioned claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10, 11, 28-33, 40-46, 63, 65-74, 80-86, 103-106, 113, 115, 117 and 114* are rejected under 35 U.S.C. 103(a) as being unpatentable over either Sonneborn (as indicated above in the rejection under 35 USC 102(b)) in view of Abo *et al.* (US 5,698,428; see entire document; henceforth Abo). *Note-this is the claim that is newly rejected under35 USC § 103(a).

Sonneborn teaches the elements set forth above in the rejections under 35 USC § 102(b). However, the chimeric nucleic acid described by Sonneborn uses ampicillin as a bacterial selection marker, and does not specifically teach using kanamycin as the bacterial selection marker (which confers resistance to genticin, a.k.a. G418).

Abo teaches that the ampicillin and kanamycin bacterial selection markers are interchangeable (see for example column 19, line 40 to column 20, line 2).

It would have been obvious to the ordinary skilled artisan to exchange the ampicillin marker used in the vector taught by Sonneborn for kanamycin because Abo teaches that these selection markers are functionally interchangeable for the selection of bacteria harboring a given plasmid. The ordinary skilled artisan would have been motivated to combine the teachings of Abo and Sonneborn in order to utilize all of the art recognized bacterial selection markers, with the benefit of minimizing the constraints on bacterial cells that can be used for the production of plasmid DNA. It is also noted that fungal cells can also be selected for in the presence of

kanamycin, thus switching the ampicillin and kanamycin genes gives an additional selection that can be used when transforming the plasmids taught by Sonneborn into fungal cells. Absent evidence to the contrary, the skilled artisan would have had an expectation of success when combining the teachings of Sonneborn and Abo because it is well known in the art that either ampicillin or kanamycin can be used as a selection marker.

Claims 1, 10, 11, 28-33, 40, 42-46, 63-67, 69-74, 80-86, 103-106, 113,115, 117 and 114* are rejected under 35 U.S.C. 103(a) as being unpatentable over either Stoldt (as indicated above in the rejection under 35 USC 102(b)) in view of Abo *et al.* (US 5,698,428; see entire document; henceforth Abo). *Note-this is the claim that is newly rejected under35 USC § 103(a).

Stoldt teaches the elements set forth above in the rejections under 35 USC § 102(b). However, the chimeric nucleic acid described by Stoldt uses ampicillin as a bacterial selection marker, and does not specifically teach using kanamycin as the bacterial selection marker (which confers resistance to genticin, a.k.a. G418).

Abo teaches that the ampicillin and kanamycin bacterial selection markers are interchangeable (see for example column 19, line 40 to column 20, line 2).

It would have been obvious to the ordinary skilled artisan to exchange the ampicillin marker used in the vector taught by Stoldt for kanamycin because Abo teaches that these selection markers are functionally interchangeable for the selection of bacteria harboring a given plasmid. The ordinary skilled artisan would have been motivated to combine the teachings of Abo and Stoldt in order to utilize all of the art recognized bacterial selection markers, with the benefit of minimizing the constraints on bacterial cells that can be used for the production of

plasmid DNA. It is also noted that fungal cells can also be selected for in the presence of kanamycin, thus switching the ampicillin and kanamycin genes gives an additional selection that can be used when transforming the plasmids taught by Stoldt into fungal cells. Absent evidence to the contrary, the skilled artisan would have had an expectation of success when combining the teachings of Stoldt and Abo because it is well known in the art that either ampicillin or kanamycin can be used as a selection marker.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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